REMARKS

Claims 4, 13 and 17-27 were pending in the present application. Claims 4, 13,.18-20, 22 and 25 have been amended. Claim 17 has been canceled. Accordingly, claims 4, 13 and 18-27 will be pending after entry of the instant amendment.

The Examiner indicates in the Office Action dated that "claim 13 is withdrawn as being drawn to a non-elected invention." Applicants respectfully submit that Group II of the restriction requirement in parent application U.S. Serial No. 09/689,992 included claim 4, "drawn to a substantially pure RDE-1 polypeptide, ***and a method of preparing an RNAi agent by incubating dsRNA in the presence of RDE-1 and RDE-4 polypeptides***". Claim 13 of the parent application was ***not included in group II***, although being drawn to "a method of preparing an RNAi agent by incubating dsRNA in the presence of RDE-1 and RDE-4 polypeptides." Notably, ***claim 13 was not included in any group of the restriction requirement in parent application U.S. Serial No. 09/689,992***. Applicants respectfully re-assert that claim 13 was intended to be included in group II but inadvertantly not recited and, accordingly, should be included in the subject matter of group II of parent application U.S. Serial No. 09/689,992 for the purposes of the instant divisional patent application.

Support for the newly added claims can be found throughout the specification including the originally filed claims. In particular, support for the recitation of "wherein the polypeptide mediates RNA interference" can be found at least at page 9, lines 14-15, and in Examples 4-10 at pages 34-47. No new matter has been added.

Rejection of Claims 4 and 17-27 Under 35 U.S.C. § 101

The Examiner has rejected claims 4 and 17-27 under 35 U.S.C. §101 because, according to the Examiner, "the claimed invention is not supported by either a substantial or credible asserted utility or a well established utility." In particular, the Examiner alleges that "[i]n page 2 of the specification applicant refers to RDE-1 polypeptides as RNAi pathway components which provide activities necessary for interference... [h]owever the specification does not identify said activities." The Examiner is of the opinion that "based on the specification and the state of the prior art at the time of filing, while the examiner fully appreciates that rde-1 gene is positively

identified as a constituent of RNAi pathway, she fails to find a credible and substantial utility for the expression product of said gene namely RDE-1 polypeptide."

Applicants respectfully traverse the foregoing rejection for the following reasons. It is Applicants' position that, based on the guidelines set forth in the *Revised Interim Utility Guidelines Training Materials* (in particular, Example 3 at pages 27-29), the present invention has a *specific and substantial utility which is credible.* Specifically, Applicants have made an assertion of utility for the specifically claimed invention, *e.g.*, using the RDE-1 protein of the present invention in mediating or enhancing genetic interference, *e.g.*, using the RDE-1 protein in the preparation of an RNAi agent (for example, by incubating a dsRNA *in vitro* in the presence of RDE-1 and RDE-4 or by transgenesis of the *rde-1* and/or *rde-4* coding sequences into a target cell) (see, for example, page 2, lines 18-19 and lines 22-23; page 4, line 31 through page 5, line 9; page 6, lines 14-20; page 9, lines 14-15; page 27, lines 14-20; page 28, lines 22-31; and Examples 8-10 at page 44, last paragraph through page 47, first paragraph of the specification). Further, Applicants have made an assertion of the utility for the RDE-1 protein in, *e.g.*, generating and testing anti-RDE-1 antibodies which can be used to study the RNAi pathway (see, for example, page 3, lines 19-21; and page 17, line 13 through page 20, line 20 of the specification), and identifying additional proteins or RNA molecules which bind to the RDE-1 protein and facilitate genetic interference, *e.g.*, by using strains harboring mutations in the *rde-1* gene or by employing a yeast two-hybrid screen (see, for example, page 3, lines 29-31; page 20, lines 27-29; page 21, lines 7-8 of the specification). Use of protein to prepare an RNAi agent of the invention is clearly a use that depends upon the particular protein, RDE-1, disclosed in Applicants' specification (similar to a use of a protein for treating Alzheimer's Disease, the example provided at pages 27-29 of the *Revised Interim Utility Guidelines Training Materials*). Therefore, the asserted utility is *specific.*

Furthermore, the asserted utility is *substantial.* Since mediating or enhancing genetic interference is a desirable outcome based upon a need in the art, the disclosed use of the claimed protein is a substantial and a "real world" use (similar to a use of a protein for treating Alzheimer's Disease, the example provided at pages 27-29 of the *Revised Interim Utility Guidelines Training Materials*).

The asserted specific and substantial utility is *credible.* "A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use." *Revised Interim Utility Guidelines*

Training Materials, page 5. In the present case, ***Applicants have taught that the RDE-1 protein of the present invention is required for genetic interference*** (see, *e.g.*, Example 4 of the specification) and, moreover, have taught a specific activity of RDE-1 in mediating genetic interference. For example, Applicants provide experimental data showing that RDE-1 is not necessary for dsRNA uptake, transport or stability in genetic interference (see, *e.g.*, Example 5 at pages 38-40 and, in particular, at page 39, lines 10-15). Applicants show that ***RDE-1 is required for the formation of extragenic interfering agents*** in the *C. elegans* germline, and, moreover, is not required for subsequent interference mediated by said agents (see, *e.g.*, Examples 8-10 of the specification). Accordingly, the instant specification teaches that the claimed RDE-1 polypeptides can be used to prepare an RNAi agent, for example, by incubating a dsRNA *in vitro* in the presence of RDE-1 and RDE-4 or by transgenesis of the *rde-1* and/or *rde-4* coding sequences into a target cell (see, for example, page 2, lines 18-19 and lines 22-23; page 4, line 31 through page 5, line 9; page 6, lines 14-20; page 9, lines 14-15; page 27, lines 14-20; page 28, lines 22-31; and Examples 8-10 at page 44, last paragraph through page 47, first paragraph of the specification). Moreover, the specification teaches that the claimed RDE-1 polypeptides can be used, *e.g.*, in generating anti-RDE-1 antibodies or *rde-1* mutants, which are useful for studying the RNAi pathway, *e.g.*, in *C. elegans* and other organisms. Thus, the RDE-1 polypeptides of the claimed invention provide novel tools for mediating and enhancing genetic interference, *e.g.*, novel tools for preparing an RNAi agent, as well as novel research tools for studying the RNAi pathway.

As the Examiner is aware, an Applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). "Instead, evidence will be sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true." M.P.E.P. §2164.07. Based on the ample teachings in Applicants' specification regarding the role and importance of RDE-1 in mediating genetic interference, Applicants respectfully submit that a person of ordinary skill in the art would conclude that Applicants' asserted utility is more likely than not true, which is all that is required under 35 U.S.C. §101.

In view of all of the foregoing, Applicants respectfully submit that the RDE-1 polypeptides of the instant invention have a *specific, substantial,* and *credible utility* that would

have been readily apparent to one of ordinary skill in the art, namely, the use of RDE-1 polypeptides in mediating and enhancing RNAi, *e.g.*, for preparing RNAi agents *in vitro* and *in vivo*. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing §101 rejection of claims 4 and 17-27.

A. Claims Rejections Under 35 U.S.C. §112, First Paragraph

(1) Rejection of Claims 4 and 17-27 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 4 and 17-27 under 35 U.S.C. §112, first paragraph as failing to adequately teach how to use the instant invention. The Examiner argues that "since the claimed invention is not supported by either a substantial or credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Applicants respectfully traverse the foregoing rejection because, as indicated above, the claimed invention has a well established utility and, thus, one of skill in the art would know how to use the claimed invention. Moreover, Applicants' specification discloses *ample* guidance as to how one of skill in the art would use the RDE-1 polypeptides of the present invention for mediating or enhancing RNAi, *e.g.*, for preparing an RNAi agent, and for studying the RNAi pathway (see, for example, the methods for preparation of RNAi agents and for ectopic expression of *rde-1*, techniques for preparing anti-RDE-1 antibodies, screening assays for identification of other RNAi pathway components, molecules that inhibit the RNAi pathway and compounds that bind to RNAi pathway proteins/genes taught by Applicants at page 17, line 13, through page 29, line 12 of the specification).

In view of the foregoing, Applicants respectfully submit that the ordinary skilled artisan would be able to make and use the claimed invention using routine experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing section 112, first paragraph rejection.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claim 4

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite based on the recitation of the phrase "high stringency." The Examiner contends that "[i]n page 11 of the specification some examples of 'high stringency' conditions are provided but said examples do not specifically define the term used in claim 4."

In the interest of expediting prosecution, claim 4 has been amended to specify that the high stringency hybridization conditions are "at 68°C in 5x SSC/5x Denhardt solution/1.0% SDS, followed by washing in 0.2x SSC/0.1% SDS at room temperature." Thus, Applicants respectfully submit that this rejection is now moot.

Claims 25-26

Claims 25-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite based on the recitation of the phrase "RDE-1 mutation." The Examiner contends that "RDE-1 in the specification is referred to [the] expression product of [the] rde-1 gene" and that "it is unclear how a polypeptide can complement a mutated "RDE-1 mutated" polypeptide."

Claim 25 (and claim 26, which depends therefrom) has been amended so as to be directed to "a substantially pure RDE-1 polypeptide encoded by a nucleic acid molecule which can complement an rde-1 mutation." Thus, Applicants respectfully submit that this rejection is now moot.

Claim 17

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite based on the recitation of the phrase "the polypeptide of claim 4, which hybridizes... ." The Examiner contends that "it is indefinite as how [a] polypeptide can hybridize under recited conditions." Claim 17 has been canceled, thereby rendering this rejection moot.

Rejection of Claims 4, 17-22 and 25-27
Under 35 U.S.C.§ 112, First Paragraph, Written Description

The Examiner has rejected claims 4, 17-22 and 25-27 under 35 U.S.C. 112, first paragraph as containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner alleges that

> [n]o ***functional description*** has been provided of the homologous sequences shown for parts 1-4 above. No information, beyond the characterization of SEQ ID NO:3 has been provided by applicants which would indicate that they had possession of the claimed genera of modified polypeptides. The specification does not contain any disclosure of the ***function*** of all the variant polypeptide sequences derived from SEQ ID NO:3 that are within the scope of the claimed genus. Therefore ***many functionally unrelated polypeptides are encompassed within the scope of these claims***.

The Examiner further alleges that "the specification discloses only **a single species** of the claimed genus (SEQ ID NO:3) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus."

Applicants respectfully traverse this rejection for the following reasons. Applicants respectfully submit that the instant specification discloses a sufficient number of examples of variants of SEQ ID NO: 3 to support a genus of SEQ ID NO: 3 variants. It is a well established principle of U.S. Patent Law that "[a] specification may, within the meaning of 35 U.S.C., § 112, First Paragraph, contain a written description of a broadly written claimed invention ***without describing all species that claim encompasses***." Utter v. Hiraga, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). Moreover, "a 'representative number' is an ***inverse function of the skill and knowledge in the art***. Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the Applicant was in possession of the ***necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed***." (see MPEP 2163(II.A.3.a.ii).

It is Applicants' position that the claimed genus of the polypeptide molecules of the present invention is defined by structural and functional features that are described in the

specification, recited in the claims, and commonly possessed by its members. In particular, the structure of the claimed genus is taught in the specification, *i.e.*, the sequence of the polypeptide of the invention (SEQ ID NO:3) as well as the sequence of the nucleic acid molecules encoding this polypeptide (SEQ ID NO:2). Applicants submit that the instant specification further teaches distinguishing structural features within the claimed genus, *e.g.*, a highly conserved carboxy-terminal region (see, *e.g.*, page 41, lines 21-26 and Figure 4B).

Further, contrary to the Examiner's assertion, Applicants describe in the present specification that a ***critical common functional feature*** of the claimed polypeptides is the ***ability to mediate RNA interference, i.e., RNAi,*** as required by the claims as currently amended. Given the foregoing features, one of ordinary skill in the art is put in possession of a plethora of variants of SEQ ID NO: 3 that are useful for mediating or enhancing RNAi. Indeed, the specification provides ample teaching as to the sequence and structure of variants of SEQ ID NO: 73 as well as methods for identifying such variants (see, for example, pages 10-12 and, in particular, page 11, line 14 through page 12, line 6 of the specification; and Example 6, at pages 40-42). Moreover, as discussed above with respect to utility, the specification provides ample teaching as to the activity of RDE-1 in mediating RNAi, and provides extensive guidance for how to test an RDE-1 polypeptide for such activity. For example, Applicants teach that RDE-1 variants can be identified by testing for complementation of mutants described in the Examples of the specification with a nucleic acid sequence encoding a variant of SEQ ID NO: 3 (see, for example, page 11, lines 15-19, and Examples 8-10 at pages 44-47 of the specification). Applicants further submit that methods of inhibiting expression of a target gene in a cell using dsRNA were known in the art at the time the application was filed (e.g., see U.S.S.N. 09/215,247, which is incorporated in the present specification by reference). Thus, the relevant skill and knowledge in the art was high such that a skilled artisan could easily recognize if a protein encoded by a variant of SEQ ID NO: 3 is able to mediate RNAi. Thus, based on the present specification and common knowledge in the art, one of ordinary skill in the art would have recognized that Applicants were in possession of the claimed invention at the time of filing.

Indeed, it is firmly established that the descriptive text needed to meet the Written Description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). In *Capon*, the Federal Circuit explained that "since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with

differences in the state of knowledge in the field and differences in the predictability of the science." *Id.* Specifically, the Court stated that:

> Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter ***depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.*** *Id.* at 1359 (emphasis added).

The Court further explained that "the written description may be satisfied 'if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.'" *Id.* (citing *Amgen Inc. v. Hoechst Marion Roussel*, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003) (emphasis added)). Accordingly, "[a]s each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." *Id.* at 1358.

Based on the foregoing considerations and framework for written description articulated by the Federal Circuit, the subject matter of the pending claims is fully described in accordance with 35 U.S.C. §112, first paragraph, by the present specification. For example, with respect to the existing knowledge in the field at the time the present application was filed, it was well-known how to recognize variants of SEQ ID NO: 3, *e.g.*, variants with 80%, 95% or 98% identity to SEQ ID NO:3 or that are encoded by a nucleic acid that hybridizes under high stringency conditions to the complement of SEQ ID NO:2. The relevant skill and knowledge in the art was high such that an artisan could easily screen for and identify homologs of *C. elegans* rde-1. Further, the level of skill in the art and the maturity of the technology of introducing nucleic acids into cells or organisms, *e.g.*, *C. elegans*, and methods of inhibiting expression of a target gene in a cell using dsRNA, were high at the filing date of the present application.

Accordingly, for at least the foregoing reasons, it would have been clear to one of ordinary skill in the art based on the teachings of present specification that Applicants were in possession of the claimed invention at the time of filing. Applicants, therefore, respectfully request that the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, for lack of written description be reconsidered and withdrawn.

Rejection of Claims 17-22
Under 35 U.S.C.§ 112, First Paragraph, New Matter

The Examiner has rejected claims 17-22 under 35 U.S.C. 112, first paragraph as allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner alleges that "[t]he terms '80%, 95%, 98%, and [the] phrase[s] 'at least 30 contiguous amino acids', and 'residues 203-1021' in claims 17-22 respectively, were not found to have support in the specification as originally filed." The Examiner concludes that claims 17-22 contain new matter.

With respect to recitation of the terms 80%, 95% and 98% in claims 18, 19 and 20, respectively, Applicants respectfully traverse this rejection. Applicants respectfully submit that support for these terms can be found at least at page 3, lines 6-8 of the specification, where the specification teaches that "the hybridizing portion of the hybridizing nucleic acid is 80%, more preferably 95%, or even 98% or 100% identical to the sequence of a portion or all of a nucleic acid encoding an RDE-1 polypeptide."

With respect to the phrase "at least 30 contiguous amino acids" in claim 21, Applicants respectfully traverse this rejection. Applicants respectfully submit that support for this phrase can be found at least at page 17, line 31 through page 18, line 1 of the specification, where the specification teaches that "[t]he antigenic peptide of an RNAi pathway protein comprises at least 8 (preferably 10, 15, 20, or 30) amino acid residues."

With respect to recitation of the phrase "residues 203-1021" in claim 22, the claim has been amended so as to be directed to a fragment comprising "amino acids 203 to ***1020*** of SEQ ID NO:3." Support for the amendment can be found at least in: Figure 4B, which depicts regions of homology between the predicted sequence of RDE-1 and four related proteins, said regions spanning from amino acids 203 to 1020 of the RDE-1 polypeptide; in the description of Figure 4B at page 7, line 30 through page 8, line 1, (as amended in the Preliminary Amendment filed August 20, 2003); and in the polypeptide sequence set forth in SEQ ID NO:13, which is a polypeptide 818 amino acids in length corresponding to amino acids 203-1020 of the RDE-1 polypeptide (SEQ ID NO:3).

In view of the foregoing, Applicants respectfully request that this rejection of the pending claims under 35 U.S.C. § 112 be reconsidered and withdrawn.

CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

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Respectfully submitted,

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